REMARKS

Claims 1-36 were pending. Claims 23-36 are withdrawn from consideration. Claims 5 and 9 are canceled, without prejudice to renewal or refiling of the original scope. Claims 1 and 10 are amended.

An abstract of the invention is provided herewith, corresponding to the published abstract of WO 2004/040009. Withdrawal of the objection is requested.

35 USC §112, second paragraph

Claims 1-22 have been rejected under 35 U.S.C. 112, second paragraph. Claim 1 has been amended to include a correlating step to accomplish the preamble of the claim. Claims 5 and 9 have been cancelled, rendering moot rejections of these claims.

In view of the above amendments, withdrawal of the rejection is requested.

35 USC §103(a)

Claims 1-22 have been rejected under 35 USC §103(a) as unpatentable over the combination of Urban in view of Blackman.

The Examiner alleges that it would have been obvious to one of ordinary skill in the art to modify the method of Urban to identify a compound which inhibits infectivity of a protozoan pathogen, since Urban teaches rhomboid assay methods and Blackman teaches that parasitic proteolytic enzymes play an essential role in invasion.

However, for the reasons set out below, one of ordinary skill in the art could not combine the teachings of Blackman and Urban to arrive at the present invention without inventive insight.

The present invention relates to the discovery that rhomboid proteases play an important role in the infectivity of protozoan pathogens and inhibitors of these rhomboid proteases may be useful in the treatment of pathogen infection.

Rhomboids are a family of serine proteases which cleave within the transmembrane domains of specific protein substrates (i.e. intramembrane proteases). Characteristic

features of Rhomboids are described in some detail from page 2 line 29 to page 5 line 6 of the application. None of the other known families of intramembrane proteases (i.e. presenilins, site 2 proteases (S2P) and signal peptide peptidases (SPP)) are serine proteases (i.e. they lack the characteristic sequence motifs and reaction mechanism of serine proteases).

Blackman is concerned with the identification of a single copy *P. falciparum* gene which encodes a protease (PfSUB1).

PfSUB1 is a member of the subtilisin familiy of proteases. This is clear from the name '*P. falciparum*-subtilisin-like protease 1' and is confirmed repeatedly in the text, for example at page 2 line 1 which states:

> *a novel single copy P. falciparum gene (denoted pfsub-1) encoding a member of the subtilisin-like serine protease superfamily (subtilases).*

Subtilisin-like proteases are a completely different family of proteases from Rhomboids and a protease of the subtilisin family is, by definition, not a Rhomboid.

The differences between PfSUB1 and Rhomboids are clear from the teaching of Blackman. In contrast to rhomboids, which have at least 4 transmembrane domains (page 3 lines 28-31 of the application), and typically 6 or 7, PfSUB1 lacks either a transmembrane domain or a GPI signal sequence (page 23402 col 2 lines 1 to 2 of Blackman). The mature PfSUB1 protease is therefore not membrane bound and the catalytic triad residues (Asp374, His430 and Ser608) are not positioned within a membrane, so PfSUB1 cannot have any intramembrane proteolysis activity. By contrast, the residues of the Rhomboid catalytic triad (Asn:Ser:His) are all located in transmembrane domains of the polypeptide, conferring intramembrane proteolysis activity.

Since it has the activity and structural motifs of a subtilisin protease, the parasitic proteolytic enzyme (PfSUB1) disclosed in Blackman is not a rhomboid. Blackman is, in fact, entirely silent about rhomboids and one of ordinary skill in the art would find no teaching or suggestion in Blackman that rhomboids play any part in protozoan invasion.

Neither could one of ordinary skill in the art extrapolate the teachings of Blackman to rhomboids, since Blackman is concerned with an entirely different family of protease (i.e. subtilases) which differ significantly in both structure and activity from rhomboids. In the light of these differences, the skilled artisan would have no reasonable expectation that teachings about subtilases might also be relevant to rhomboids.

Since neither Urban nor Blackman teaches or suggests any role for rhomboids in protozoan infectivity, one of ordinary skill in the art would have no reason or motivation to employ the rhomboid assays of Urban to identify compounds which inhibit this process. Furthermore, in the absence of even a suggestion in the art that rhomboids might be involved in protozoan infectivity, the skilled artisan could have no reasonable expectation of success, even if such an assay were attempted.

For the reasons set out above, one of ordinary skill in the art could not combine the teachings of Blackman and Urban to arrive at the present invention. The present claims are therefore non-obvious over the combination of Urban and Blackman and meet the requirements of 35 USC 103(a). Reconsideration of the rejection is therefore requested.

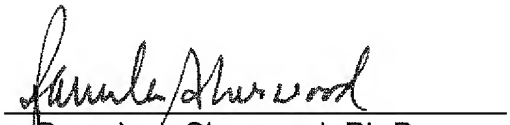
CONCLUSION

Applicant submits that all of the claims are now in condition for allowance, which action is requested. If the Examiner finds that a Telephone Conference would expedite the prosecution of this application, he is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any other fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815, order number MEWE-022.

Respectfully submitted,

Date: March 12, 2007

By: 
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